18. *Triterpenoids. Part V.* Some Relative Configurations in Rings* C, D, *and* E *of the* β*-Amyrin and the Lupeol Group of Triterpenoids.*

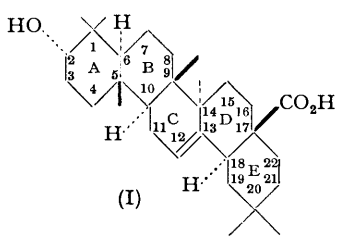
By D. H. R. Barton and N. J. Holness.

Relative configurations have been assigned to asymmetric centres at positions 10, 11, 12, 13, 14, 16, 17, 18, 19, and 20 in the β-amyrin group of triterpenoids. 18-*iso*Oleanolic acid, methyl olean-10-enolate acetate, methyl 11-keto-oleananolate acetate and a number of other derivatives of oleanolic acid have been prepared. The lactonisation of oleanolic and morolic acids has been investigated.

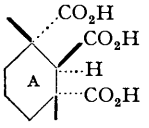
The synthesis of " betulin triol diacetate," starting with siaresinolic acid, is reported. This has enabled configurations to be assigned at $C_{(13)}$ and $C_{(18)}$ in the lupeol group of triterpenoids. Together with earlier work, this permits relative configurations to be assigned also at $C_{(10)}$, $C_{(14)}$, and $C_{(19)}$.

Some experiments in the ursolic acid series are reported.

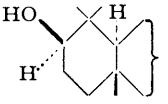
When this work on the stereochemistry of the pentacyclic triterpenoids was initiated knowledge of the subject was meagre. Giacomello (*Gazzetta*, 1938, **68**, 363) had reported an *X*-ray analysis of certain members of the β-amyrin group from which he had concluded that all five rings were fused *trans-anti-trans* to each other. This would imply the stereochemical relationships summarised in the formula (I) for oleanolic acid. The almost ubiquitous hydroxyl group at $C_{(2)}$ was placed by Giacomello as indicated in (I) and this assignment of configuration was tentatively confirmed by Ruzicka and Gubser (*Helv. Chim. Acta*, 1945, **28**, 1054) from a study (*a*) of the rates of alkaline hydrolysis of β-amyrin acetate and *epi*-β-amyrin acetate and (*b*) of molecular models of the Stuart type. However, as shown in the sequel, Giacomello's conclusions are incorrect in at least two respects.



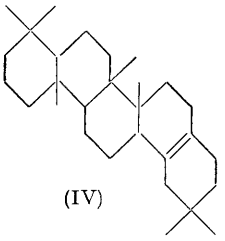
(I)



(II)



(III)



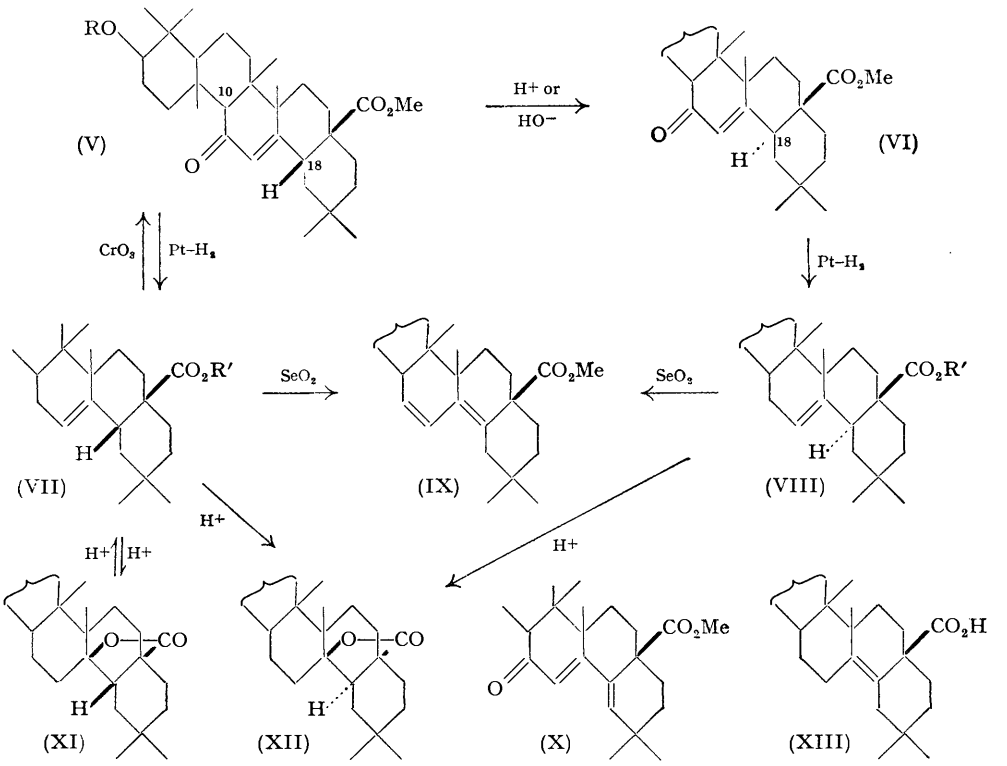
(IV)

A study of the properties of the $C_{11}H_{16}O_6$ tricarboxylic acid obtained by vigorous oxidation of abietic acid enabled Barton and Schmeidler (*J.*, 1948, 1197; 1949, S 232) to conclude that the C_{11} acid had the configuration shown in (II). In view of the relations which have been established between abietic acid and other diterpenoids on the one hand and between abietic acid and the triterpenoids on the other (for summaries see Barton, *Quart. Reviews*, 1949, **3**, 36; Jeger, " Fortschritte der Chemie organischer Naturstoffe," 1950, Vol. VII) it can be concluded that, provided that there is no inversion during the genesis of (II), rings A and B of oleanolic acid are fused *trans* to each other. With regard to the configuration of the hydroxyl at $C_{(2)}$ consideration of (*a*) the relative stabilities of the β- and *epi*-β-amyrin, (*b*) the relative degree of steric hindrance in the two alcohols, and (*c*) elimination evidence, all considered in the light of the concept of equatorial and polar bonds (see Barton and Rosenfelder *J.*, 1951, 1048), enabled one of us (Barton, *Experientia*, 1950, **6**, 316) to conclude that this hydroxyl group had the *opposite* configuration in β-amyrin and its congeners to that assigned by Giacomello and by Ruzicka. The stereochemical data for ring A in the β-amyrin series relative to an arbitrary configuration at $C_{(5)}$ can, then, be summarised as in partial formula (III).

As bearing on the practical work now reported it is convenient to turn next to the stereochemistry of rings D and E in oleanolic acid. As has been emphasized previously

* Part IV, *J.*, 1951, 3147.

(Barton and Brooks, *J.*, 1951, 257; Davy, Halsall, and Jones, *Chem. and Ind.*, 1951, 233) the carboxyl group in this acid must be polar in the stereochemical sense. This conclusion, however, still permits *cis*- or *trans*-fusion of rings D and E. The argument of Bilham and Kon (*J.*, 1940, 1469) that this fusion is *cis* would appear to be invalidated by the new formulation (IV) (Barton and Brooks, *loc. cit.*) for oleanene II. We have provided a final solution to the problem by the reactions summarised below (see also Barton and Holness, *Chem. and Ind.*, 1951, 233). Kitasato (*Acta Phytochim.*, 1934, **8**, 1) found that methyl 11-keto-oleanolate acetate (V; R = Ac) was isomerised to methyl ψ-11-keto-oleanolate acetate (VI; R = Ac) by treatment with hydrogen bromide in acetic acid. We find that this change can also be effected by alkali (cf. the corresponding isomerisation in the β-amyrin series; Picard and Spring, *J.*, 1940, 1198; Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 758; Budziarek, Johnston, Manson, and Spring, *Chem. and Ind.*, 1951, 478). Clearly the asymmetric centres at $C_{(10)}$ and/or $C_{(18)}$ are inverted by enolisation. Just as catalytic hydrogenation of methyl 11-keto-oleanolate acetate gives methyl oleanolate acetate (VII; R = Ac, R′ = Me), so the similar reduction of methyl ψ-11-keto-oleanolate acetate gave the methyl ester acetate, m. p. 250—252°, $[\alpha]_D$ + 44°, of a new triterpenoid hydroxy-acid. This was shown to be methyl 18-*iso*oleanolate acetate

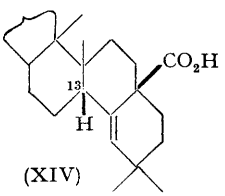


(VIII; R = Ac, R′ = Me), differing from ordinary methyl oleanolate acetate only in its configuration at $C_{(18)}$, for on oxidation by selenium dioxide it gave methyl dehydro-oleanolate acetate (IX; R = Ac) (see Barton and Brooks, *loc. cit.*), prepared in a similar way (Ruzicka, Grob, and van der Sluys-Veer, *Helv. Chim. Acta*, 1939, **22**, 788) by oxidation of methyl oleanolate acetate. This shows that the configuration at $C_{(18)}$ in oleanolic acid is unstable; therefore, the D–E fusion must be *cis* (see further discussion below). The formation of (IX; R = Ac) by reduction with sodium and alcohol and subsequent acetylation of both (V; R = Ac) and (VI; R = Ac) is further proof (Kitasato, *loc. cit.*) for the postulated inversion at $C_{(18)}$ but *not* at $C_{(10)}$. Further evidence supporting this conclusion is the fact that the dienone (X; R = Ac), where $C_{(18)}$ is no longer asymmetric, cannot be

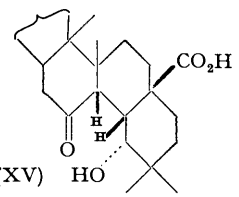
isomerised by alkali (see Experimental). These experiments also imply that rings B and C must be fused in the more stable arrangement. An even more convincing proof of this has been given recently by Budziarek *et al.* (*loc. cit.*).

Additional, and more subtle, evidence for our conclusion that rings D and E are *cis*-fused in oleanolic acid was obtained in the following way. Oleanolic acid (VII; R = R′ = H), on treatment in chloroform solution with a stream of hydrogen chloride, gave an equilibrium mixture of the free acid (76%) and its true lactone (XI; R = H) (24%), the same equilibrium mixture being obtained on treating the lactone itself in the same way. The equilibrium appears to be set up almost instantaneously and therefore the reaction velocity both to *and from* (XI; R = H) must be large. Now it has been shown conclusively (Davy, Halsall, and Jones, *J.*, 1951, 458) that, thermodynamically, the double bond position in δ-oleanolic acid (XIII; R = H) must be much more stable than in oleanolic acid itself (VII; R = R′ = H) or in 18-*iso*oleanolic acid (VIII; R = R′ =H). Since the composition of the equilibrium mixture of oleanolic acid and its lactone remains unchanged even after 17 hour's treatment with chloroformic hydrogen chloride it is clear that the rate of opening of the lactone ring to give the more stable (XIII; R = H) must be very much slower (by a factor of at least 10^4) than the opening to regenerate oleanolic acid (VII; R = R′ = H). In our opinion this remarkable difference demands the steric explanation that the formation of (XIII; R = H) is not favoured kinetically because it would represent *cis*-elimination in an *ionic* reaction. In contrast, treatment of 18-*iso*-oleanolic acid acetate with chloroformic hydrogen chloride afforded irreversibly the corresponding lactone (XII; R = Ac) which is, therefore, much more stable thermodynamically than the ordinary lactone. Surprisingly, this 18-*iso*-lactone acetate is, in fact, the compound frequently referred to in the literature as " oleanolic acid lactone acetate " (Winterstein and Stein, *Z. physiol. Chem.*, 1931, **199**, 64). Thus reaction of oleanolic acid acetate, or of the derived 18-*n*-lactone, with hydrogen bromide in acetic acid or with refluxing hydrochloric–acetic acid—reagents which have a far greater proton-donating power than chloroformic hydrogen chloride—afforded the long known 18-*iso*lactone acetate. A number of other lactones reported in the literature, *e.g.*, that of hederagenin, must also be 18-*iso*-compounds.

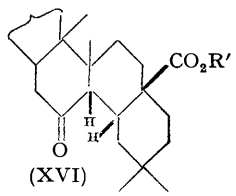
The above evidence enables configurations to be assigned to $C_{(17)}$ and $C_{(18)}$ in oleanolic acid. In Part I of this series (Barton and Brooks, *loc. cit.*), it was concluded that the configuration at $C_{(13)}$ in morolic acid was such (XIV; R = H) that the C–H bond was stereochemically polar and on the *same* side of the molecule as the carboxyl group. The partial synthesis of morolic acid from dihydro-12-ketosiaresinolic acid (XV; R = H) (Barton, Brooks, and Holness, *J.*, 1951, 277) (see further below) by Wolff–Kishner reduction, etc., shows that the configuration at $C_{(13)}$ in morolic acid must also be the thermodynamically more stable one. The same must be true in 12-keto-oleananolic acid (XVI; R = R′ = H) (see Experimental).



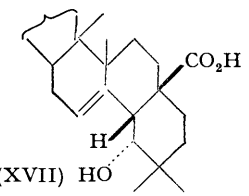
(XIV)



(XV)



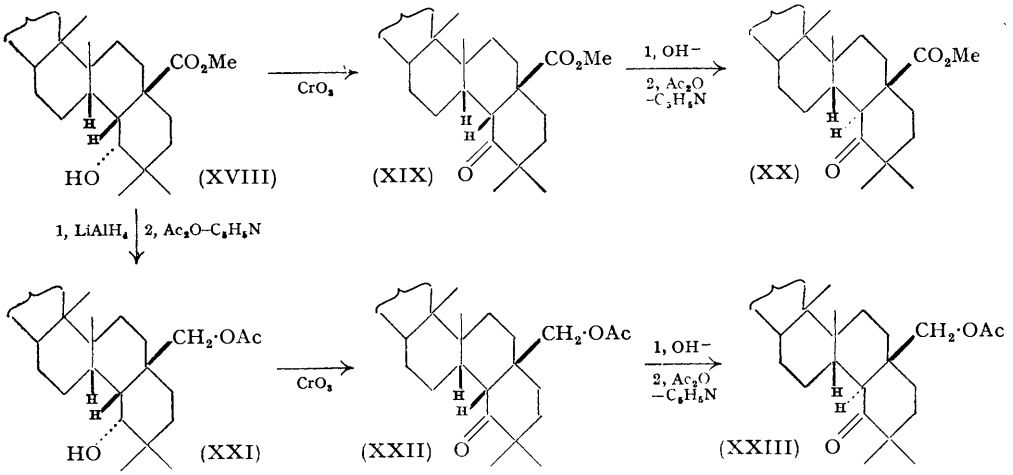
(XVI)



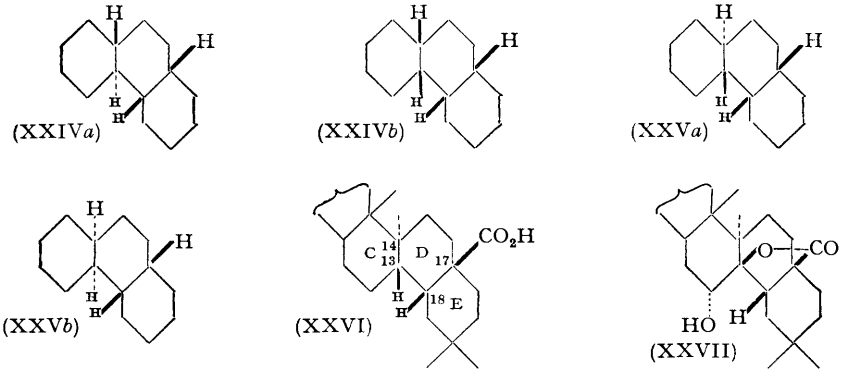
(XVII)

Our attention was directed next to the stereochemistry of rings D and E in siaresinolic acid (XVII; R = H). This acid has been related to oleanolic acid (Bilham, Kon, and Ross, *J.*, 1942, 540; Ruzicka, Grob, Egli, and Jeger, *Helv. Chim. Acta*, 1943, **26**, 1218), but only in ways which destroy the configuration at $C_{(18)}$. Siaresinolic acid was converted into methyl dihydrosiaresinolate monoacetate (XVIII; R = Ac) as described previously (Barton, Brooks, and Holness, *loc. cit*). Oxidation by chromic acid gave the corresponding ketone (XIX; R = Ac). This was shown to be a *cis*-α-decalone, for on treatment with methanolic potassium hydroxide followed by reacetylation it afforded an isomeric *trans*-

α-decalone (XX; R = Ac). In confirmation, reduction of (XVIII; R = Ac) by lithium aluminium hydride followed by reacetylation furnished the diacetate (XXI; R = Ac). This was oxidised by chromic acid to a ketone (XXII; R = Ac), which was isomerised by methanolic potassium hydroxide and then reacetylated to give the *trans*-α-decalone



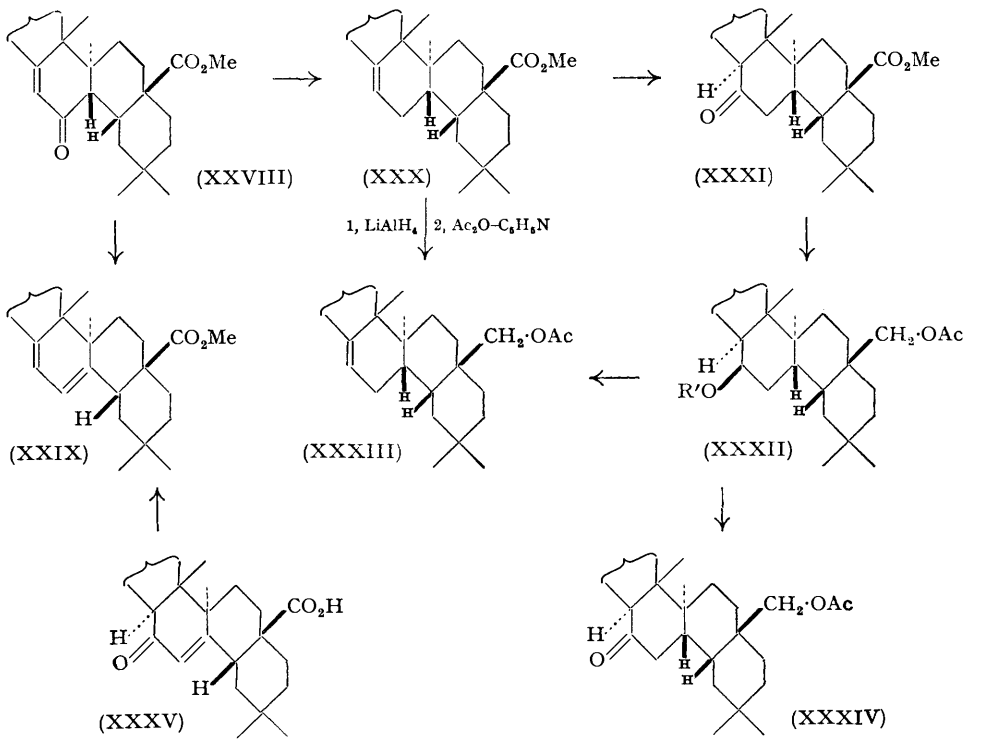
(XXIII; R = Ac). Now the properties of the hydroxyl group at $C_{(19)}$ in siaresinolic acid, in particular its resistance to esterification and its ease of elimination, show that it must be polar in the stereochemical sense (cf. Barton, *Experientia, loc. cit.*). The ease of elimination shows further (Barton, *loc. cit.*) that the $C_{(18)}$ hydrogen atom must also be polar and *trans* to the $C_{(19)}$-hydroxyl group. All these facts are accommodated by (XVII), (XVIII), etc. Incidentally, it can be argued from the failure of the carboxyl group of siaresinolic acid to lactonise with the $C_{(19)}$-hydroxyl group that the latter must, if polar, be on the side of ring E opposite to the carboxyl group. This is only possible if rings D and E are *cis*-fused. Thus all the stereochemical evidence is in agreement.



The experiments described above also appear to provide information on the relative configuration of $C_{(14)}$ with respect to $C_{(17)}$. In compounds (XV) and (XVI) the more stable arrangement of the C–D ring junction is that with the $C_{(13)}$:$C_{(18)}$ relation *syn* and the D–E ring fusion *cis*. By analogy with the important experiments by Linstead and his collaborators (*J.*, 1950, 1428 and earlier papers) as further discussed by W. S. Johnson (*Experientia*, 1951, **7**, 315) in the light of the theory of equatorial and polar bonds, it can be concluded that of the pairs of hydrocarbons, (XXIV*a*) and (XXIV*b*), and (XXV*a*) and (XXV*b*), (XXIV*a*) would be *more* stable than (XXIV*b*), and (XXV*a*) more stable than (XXV*b*). Clearly it is the latter relation which holds for rings C, D, and E in oleananolic

acid. The stereochemistry of rings D and E in this acid can, therefore, be summarised as in (XXVI).

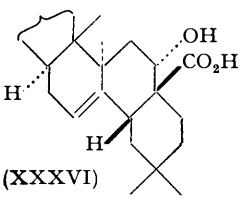
Attention was next directed to derivatives of oleananolic acid substituted at $C_{(12)}$. Ruzicka, Hösli, and Hofmann (*Helv. Chim. Acta*, 1936, **19**, 109) demonstrated that reaction of oleanolic acid acetate with perhydrol in acetic acid afforded a hydroxy-lactone, m. p. 292—294°. Because of its method of formation this compound must be formulated as (XXVII; R = Ac) with the $C_{(13)}$(–O) and the $C_{(17)}$ (–CO–) bonds polar on the same side of the ring system and the $C_{(12)}$(–OH) bond polar and on the opposite side. Picard and Spring (*J.*, 1940, 1387), later prepared a hydroxy-lactone, m. p. 333°, by the action of perbenzoic acid on oleanolic acid acetate. Since this reaction should, on a mechanistic basis, afford the same hydroxy-lactone, we repeated the preparation by both methods and, in fact, obtained the same substance, m. p.s 294—295° and then 325—328° (decomp.) after re-solidification. The identity was confirmed by comparison of the respective diacetates. The same hydroxy-lactone was also obtained by potassium permanganate oxidation of oleanolic acid acetate (cf. Aumüller, Wedekind, and Schicke, *Annalen*, 1935, **517**, 211). The 12(polar)-hydroxyl group in this compound is *not* acetylated by cold pyridine–acetic anhydride, but is readily acetylated by this reagent during half an hour at 100°. In agreement with the assigned configuration, compounds which have the opposite, thermodynamically more stable (equatorial) hydroxyl group at $C_{(12)}$ and are prepared by sodium and alcohol reduction of the corresponding 12-ketones, are *more* readily acetylated (cf. Barton, *Experientia, loc. cit.*).



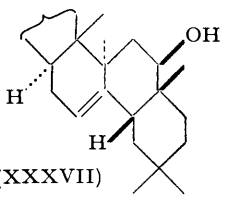
After completion of these experiments concerning $C_{(12)}$ it became important to study similarly reactions at $C_{(11)}$. Methyl 12-keto-oleananolate acetate (XVI; R = Ac, R′ = Me) was converted into the αβ-unsaturated ketone (XXVIII; R = Ac) by dehydrogenation with bromine. Catalytic hydrogenation of this ketone gave a mixture of the homoannular diene (XXIX; R = Ac) and the desired methyl olean-10-enolate acetate (XXX;

R = Ac). Since this mixture was only separable by careful chromatography a more convenient route to (XXX; R = Ac) was sought. This was found in Wolff–Kishner reduction of (XXVIII; R = Ac) followed by methylation and reacetylation. Treatment of methyl olean-10-enolate acetate, which showed an ultra-violet absorption spectrum characteristic of a triply substituted double bond, gave, with perhydrol–acetic acid, methyl 11-keto-oleananolate acetate (XXXI; R = Ac), m. p. 268—270°, $[\alpha]_D$ +3°, $\lambda_{max.}$ 292 mμ, $\varepsilon_{max.}$ = 30 (in alcohol). Lithium aluminium hydride reduction of this ketone, followed by acetylation with pyridine–acetic anhydride at room temperature, furnished the triol diacetate (XXXII; R = Ac, R′ = H). More vigorous acetylation with the same reagent at 100° gave the triacetate (XXXII; R = R′ = Ac). On treatment with phosphorus oxychloride in pyridine the hydroxy-diacetate afforded olean-10-ene-2 : 28-diol diacetate (XXXIII; R = Ac), the constitution of which was confirmed by its preparation by the reduction of (XXX; R = Ac) with lithium aluminium hydride followed by reacetylation. Chromic acid oxidation of 2 : 28-diacetoxyolean-11-ol (XXXII; R = Ac, R′ = H) gave the corresponding ketone (XXXIV; R = Ac). The constitution of (XXIX; R = Ac) was confirmed by its preparation from 11-keto-oleanolic acid acetate (XXXV; R = Ac).

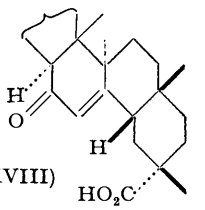
The $C_{(11)}$-hydroxyl group in 2 : 28-diacetoxyolean-11-ol is regarded as polar, (*a*) because of its hindrance to acetylation, (*b*) because of the ease of (*trans*-)elimination of water on treatment with phosphorus oxychloride in pyridine, and (*c*) because of the method of preparation.* Now, as mentioned above, the B–C and C–D ring junctures in oleananolic acid are in the more stable arrangements. Following the arguments of W. S. Johnson (*loc. cit.*), this is to be interpreted as indicating that ring C has a chair conformation. In the chair conformation of *cyclo*hexane two adjacent polar-type substituents must necessarily be *opposite* in configuration (see Barton, *Experientia*, *loc. cit.*). Since the configuration of a $C_{(12)}$-hydroxyl group, if polar, is opposite to the configuration of the $C_{(17)}$-carboxyl group (see above), the configuration of the $C_{(11)}$ polar hydroxyl group must be the *same* as that of the $C_{(17)}$-carboxyl group. Furthermore the $C_{(11)}$ polar hydroxyl group must be *trans* (see above) to the $C_{(10)}$-hydrogen atom and, therefore, the configurations shown in the formulæ (XXXI) to (XXXV) can be deduced.



(XXXVI)



(XXXVII)



(XXXVIII)

Related triterpenoids of the β-amyrin group, whose configurations in rings C, D, and E are clarified by the above work, are echinocystic acid (XXXVI; R = H) with a polar hydroxyl at $C_{(16)}$, maniladiol (XXXVII; R = H) with the opposite configuration at $C_{(16)}$, and glycyrrhetic acid (XXXVIII; R = H) whose $C_{(20)}$-carboxyl group can, apparently, lactonise on to $C_{(13)}$ (Ruzicka and Marxer, *Helv. Chim. Acta*, 1939, **22**, 195; Ruzicka and Jeger, *ibid.*, 1942, **25**, 775). Our experiments do *not* relate the configuration at $C_{(10)}$ (and hence elsewhere in rings C, D, and E) to that at $C_{(5)}$ and at $C_{(9)}$ and this problem, in our opinion, remains unsolved (cf. Gutmann, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1154). However, there would appear to be only two possibilities which will accommodate (*a*) the reactions at $C_{(11)}$ reported above and (*b*) the fact that rings B, C, and D are fused in the more stable arrangement. These are represented in Fig. 1 (B–C *cis*, $C_{(9)}$:$C_{(14)}$ *syn*,

* It seems generally true that lithium aluminium hydride reduction of a keto-group which is *not* hindered sterically affords the equatorial hydroxyl group (see, *e.g.*, Shoppee and Summers, *J.*, 1950, 687). On the other hand, similar reduction of keto-groups which are subject to marked hindrance, *e.g.*, $C_{(11)}$ in the steroid series and $C_{(11)}$ and $C_{(19)}$ in the triterpenoid series, gives the polar hydroxyl group. Evidence for the hindrance at $C_{(11)}$ in the triterpenoid series is that attempted Wolff–Kishner reduction of (XXXI; R = Ac) at 180° gave back, after methylation and reacetylation, unchanged starting material (see Experimental).

c/d *trans*) and Fig. 2 (b/c *trans*, $C_{(9)}$:$C_{(14)}$ *anti*, c/d *trans*), which depict our alternative interpretations of the stereochemistry of oleananolic acid.*

The elegant inter-relationship of lupeol and β-amyrin through a common reaction product, β-amyrene III (XXXIX) recently reported by Ames, Halsall, and Jones (*J.*, 1951, 450) and further extended to include a conversion of betulinic acid (XL; R = R′ = H) into moradiol (XLI; R = H) (Davy, Halsall, and Jones, *J.*, 1951, 2696), demonstrates identical configurations in the lupeol and the β-amyrin series so far as positions 2, 5, 6, 9, 10, 14, and 17 are concerned and shows that $C_{(13)}$ must be configurationally the same as in morolic and oleananolic acids. Davy, Halsall, Jones, and Meakins (*J.*,

Fig. 1.

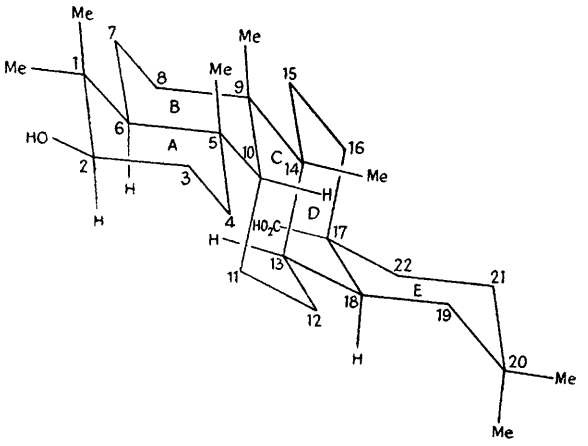
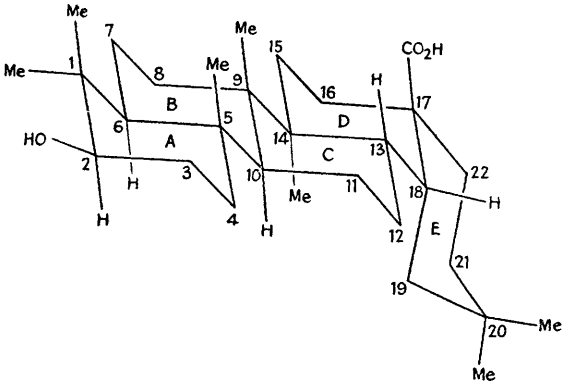


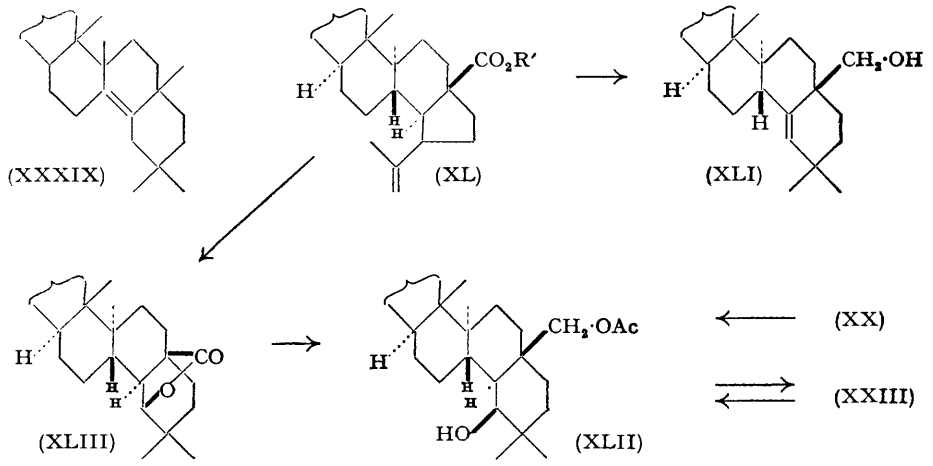
Fig. 2.



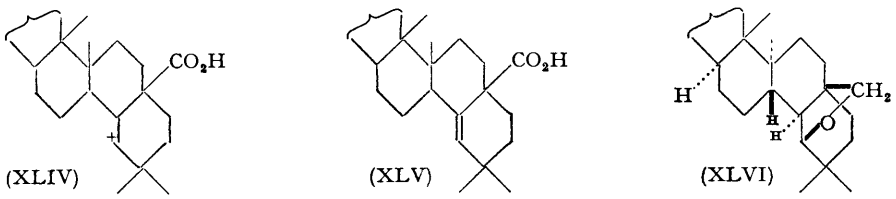
1951, 702) have recently discussed the stereochemistry at $C_{(18)}$ in the lupeol series and have concluded that the d/e ring fusion must be *trans*. Through the kindness of Professor E. R. H. Jones, F.R.S., and Dr. T. G. Halsall in informing us of their results before general publication it became possible to confirm this conclusion by the partial synthesis of the diacetate (XLII; R = Ac) by methods of stereochemical unambiguity (see Barton and Holness, *ibid.*, p. 233). Thus lithium aluminium hydride reduction of both (XX; R = Ac) and (XXIII; R = Ac), followed by reacetylation, furnished a triol diacetate (XLII; R = Ac) identical in all respects with a specimen of "betulin triol diacetate" kindly provided by Professor E. R. H. Jones and Dr. T. G. Halsall. The latter had been prepared from betulinic acid through the lactone (XLVI; R = Ac), followed by lithium aluminium hydride reduction, reactions which preserve the configuration at $C_{(18)}$ and confirm that

* It will be seen that Figs. 1 and 2 assign a definite configuration for $C_{(9)}$ relative to $C_{(5)}$. This is only a probable, not a firmly established, assignment. It is hoped to present the relevant arguments in detail in a later paper.

the unesterified hydroxyl group in (XLII; R = Ac) must be (*a*) polar in character and (*b*) on the same side of the molecule as the $C_{(17)}$-acetoxymethyl group. Chromic acid oxidation of (XLII; R = Ac) regenerated its precursor (XXIII; R = Ac).



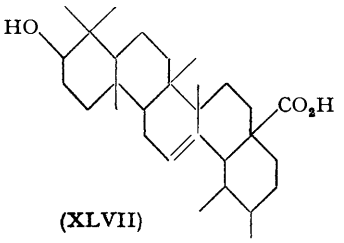
The above proof of configuration at $C_{(18)}$ in lupeol assumes that the lactone (XLIII; R = Ac) is formed from the carbonium ion (XLIV; R = Ac) *without* inversion at $C_{(18)}$. It would appear a possible criticism of this proof that the lactone formation might actually proceed through morolic acid acetate (XLV; R = Ac) (Barton and Brooks, *loc. cit.*), or that there might be an equilibrium between this acid and the lactone in a suitably acidic medium. Both possibilities were excluded in the following ways. First, treatment



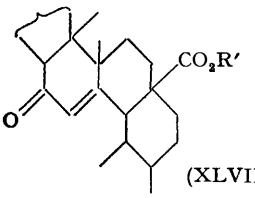
of morolic acid with hydrogen bromide in acetic acid furnished in excellent yield 18-*iso*-oleanolic acid lactone acetate (see above) which was further characterised by oxidation of the derived alcohol to the corresponding ketone. Secondly, it is well known that treatment of betulin with acetic acid containing a little sulphuric acid or with refluxing formic acid affords *allo*betulin acetate or formate respectively. The constitution of *allo*betulin has been proved (Davy, Halsall, Jones, and Meakins, *loc. cit.*) to be represented by (XLVI; R = H) by direct oxidation of its acetate to the lactone (XLIII; R = Ac). *allo*Betulin could, in principle, be formed *via* a carbonium ion [as (XLIV)] or by cyclisation of moradiol [as (XLV)]. In fact, moradiol is converted into the diacetate or diformate under the conditions, required for the production of *allo*-betulin acetate or formate. These compounds must, therefore, be formed from betulin without inversion at $C_{(18)}$.

We have not carried out extensive experiments in the α-amyrin series, but several interesting observations have been made with ursolic acid. The experiments of Ruzicka, Jeger, and their collaborators (*Helv. Chim. Acta*, 1945, **28**, 199; 1947, **30**, 140, 1294; 1949, **32**, 1075; 1950, **33**, 700, 889) have shown that the configurations at positions 2, 5, 6, 9 and, probably, 10 and 14 are the same in oleanolic and ursolic (XLVII; R = H) acids. In an effort to obtain information about the asymmetry at $C_{(18)}$ ursolic acid was treated with chloroformic hydrogen chloride. The acid was thereby equilibrated with its hitherto unknown lactone, although the equilibrium content of the lactone was only about 10%. At first, this seemed to indicate a *syn*-relation at $C_{(13)}$–$C_{(18)}$ in the lactone (cf. above).

However, reaction of methyl 11-ketoursolate acetate (XLVIII; R = Ac, R′ = Me) with either acid or base, unlike the behaviour of the corresponding 11-keto-oleanolic acid compound (see above), failed to cause isomerisation. Indeed, the ursolic acid derivative was far more stable towards these reagents than the oleanolic acid compound. We conclude either that the $C_{(18)}$ configuration is in the more stable arrangement *or* that there is no hydrogen attached to $C_{(18)}$.



(XLVII)



(XLVIII)

In connection with an *X*-ray analysis of triterpenoid compounds being undertaken in the Physics Department of this College we have prepared methyl oleanolate iodoacetate *via* the corresponding chloroacetate following the method used by Curtis (*J.*, 1950, 1017) in the lanosterol field.

Experimental

M.p.s are uncorrected. They were determined in open capillaries in the usual way unless specified to the contrary. Rotations were determined in chloroform solution. Values of $[\alpha]_D$ have been approximated to the nearest degree. Ultra-violet absorption spectra were measured in absolute ethanol solution with the Unicam S.P. 500 Spectrophotometer.

Savory and Moore's standardised alumina for chromatography was used unless specified to the contrary. Light petroleum refers to that fraction of b. p. 40—60°.

The phrase " in the usual way " implies, in general, dilution with water, extraction with ether, washing successively with aqueous potassium hydroxide (or other more suitable basic reagent), aqueous hydrochloric acid, and water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation with benzene *in vacuo*.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanol or dioxan–methanol according to the solubility of the ester.

For methylations with diazomethane the acid was treated with an excess of ethereal diazomethane. After the mixture had been kept at room temperature until the evolution of nitrogen had ceased, the excess of diazomethane and the ether were removed *in vacuo* or on the steam-bath.

Oleanolic Lactone.—Purified oleanolic acid, $[\alpha]_D$ +77° (*c*, 3·26), in chloroform (25 ml.) was treated with a stream of gaseous hydrogen chloride at room temperature and then poured into water. The product was separated into acid and neutral fractions in the usual way. The neutral fraction was characterised as *oleanolic lactone* which, recrystallised from chloroform–methanol, had m. p. 278° (decomp.), $[\alpha]_D$ +11° (*c*, 6·90), +12° (*c*, 3·08) (Found: C, 77·5; H, 10·6. $C_{30}H_{48}O_3,0{\cdot}5CH_3{\cdot}OH$ requires C, 77·45; H, 10·7%). Acetylation with pyridine and acetic anhydride overnight at room temperature afforded *oleanolic lactone acetate*; recrystallised from methanol, it had m. p. 293—295°, $[\alpha]_D$ +19° (*c*, 1·83) (Found: C, 76·65; H, 9·9. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%). The acid fraction from the equilibration was characterised as pure oleanolic acid from its m. p., mixed m. p., and rotation (where appropriate). The results are summarised in the following Table.

Wt. of oleanolic acid taken, mg.	Duration of HCl treatment	Wt. of lactone formed, mg. (%)	Wt. of recovered acid, mg.	$[\alpha]_D$ of recovered acid
190	1 min.	51 (26%)	—	—
480	15 min.	120 (25%)	370	+76° (*c*, 1·54)
400	1 hr.	95 (24%)	300	—
450	8 hr.	108 (24%)	—	—
1330	17 hr.	320 (24%)	—	+76·5° (*c*, 1·74)
190 *	1 hr.	45 (24%)	—	+76° (*c*, 1·77)

* Of oleanolic lactone.

Methyl 11-*Keto-olean*-12 : 18-*dienolate Acetate*.—Methyl 11-keto-oleanolate acetate (280 mg.), m. p. 242—244°, $[\alpha]_D$ +83° (*c*, 6·67) (Mower, Green, and Spring, *J.*, 1944, 256), was treated in 5 ml. of " AnalaR " acetic acid at 80° with three drops of 40% hydrogen bromide–acetic acid and then with 1·6 ml. of 6% bromine–acetic acid during 15 minutes. The mixture was heated for a further 45 minutes, diluted with water, and worked up in the usual way. Filtration in benzene solution through alumina, followed by recrystallisation from methanol, gave *methyl* 11-*keto-olean*-12 : 18-*dienolate acetate*, m. p. 266—268° (decomp.), $[\alpha]_D$ +258° (*c*, 2·11) (Found : C, 75·4; H, 9·3. $C_{33}H_{48}O_5$ requires C, 75·55; H, 9·15%). When this compound (100 mg.) was heated with 20 ml. of 10% potassium hydroxide in *n*-propanol under reflux for 48·5 hours, worked up in the usual way, methylated, and then acetylated, it was recovered unchanged, m. p. 265—267°, undepressed on admixture with starting material.

Methyl ψ-11-*Keto-oleanolate Acetate*.—(a) *Acid procedure* (see Kitasato, *Acta Phytochim.*, 1934, **8**, 1). Methyl 11-keto-oleanolate acetate (1 g.) in 50% hydrobromic acid–acetic acid (20 ml.) was left for 1 week. After working up in the usual way methyl ψ-11-keto-oleanolate acetate was obtained. Purified by chromatography over alumina and recrystallisation from methanol this compound had m. p. 308—309°, $[\alpha]_D$ +84° (*c*, 1·36), $\lambda_{max.}$ 248 mμ, $\varepsilon_{max.}$ 14,100 (Found : C, 74·65; H, 9·6. Calc. for $C_{33}H_{50}O_5$: C, 75·25; H, 9·6%).

(b) *Alkaline procedure*. Methyl 11-keto-oleanolate acetate (1·17 g.) in 10% potassium hydroxide–*n*-propanol (30 ml.) was refluxed for 33 hours. Dilution with water and working up in the usual way gave an acid fraction which, after methylation, acetylation, and recrystallisation, afforded methyl ψ-11-keto-oleanolate acetate identical with that prepared by Kitasato's procedure. The latter method is to be preferred.

Methyl 18-iso*Oleanolate Acetate*.—Methyl ψ-11-keto-oleanolate acetate (220 mg.) was hydrogenated in acetic acid solution overnight using a platinum catalyst. Working up in the usual way afforded *methyl* 18-iso*oleanolate acetate* (recrystallised from chloroform–methanol), m. p. 250—252°, $[\alpha]_D$ +44° (*c*, 1·96) (Found : C, 77·2; H, 9·85. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). This compound showed $\lambda_{max.}$ 199 mμ, $\varepsilon_{max.}$ 3800, ε_{215} 1100 (*c*, 0·0052), indicative of a triply substituted ethylenic linkage. In agreement, methyl oleanolate acetate itself showed $\lambda_{max.}$ 201 mμ, $\varepsilon_{max.}$ 4200, ε_{215} 1300 (*c*, 0·0091).

Methyl 18-*iso*oleanolate acetate (40 mg.) in " AnalaR " acetic acid (10 ml.) was refluxed with selenium dioxide (25 mg.) for 1 hour. The reaction product, worked up in the usual way, filtered in benzene solution through alumina, and recrystallised from chloroform–methanol, had m. p. 223—224°, $[\alpha]_D$ −128° (*c*, 0·68), $\lambda_{max.}$ 242, 252, and 261 mμ, $\varepsilon_{max.}$ 25,500, 29,100 and 18,900 respectively, and was undepressed in m. p. on admixture with an authentic specimen of methyl dehydro-oleanolate acetate, m. p. 223—224°, $[\alpha]_D$ −128° (*c*, 4·49).

18-iso*Oleanolic Acid Acetate*.—Methyl 18-*iso*oleanolate acetate (200 mg.) was heated with absolute ethanol (5 ml.) containing 200 mg. of dissolved sodium for 17 hours at 180°. The reaction product, worked up and acetylated in the usual way, gave 18-iso*oleanolic acid acetate* (recrystallised from methanol), m. p. 270—272°, $[\alpha]_D$ +50° (*c*, 2·40) (Found : C, 77·25; H, 10·6. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%).

18-iso*Oleanolic Lactone Acetate*.—18-*iso*Oleanolic acid acetate (80 mg.) in chloroform (10 ml.) was treated with a stream of dry hydrogen chloride for 30 minutes. Working up in the usual way gave 18-iso*oleanolic lactone acetate* (no acid fraction), m. p. 340—345° (decomp.) (recrystallised from chloroform–methanol), $[\alpha]_D$ +23° (*c*, 1·45) (Found : C, 76·95; H, 10·3. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%). The lactone was quantitatively recovered unchanged after 530 hours in chloroform saturated with hydrogen chloride. No trace of acid was produced. Under the same conditions oleanolic acid (60 mg.) gave the lactone (14 mg., 24%) in the usual equilibrium proportion.

Alkaline hydrolysis of the acetate lactone in the usual way gave 18-iso*oleanolic lactone* which, recrystallised from methanol, had m. p. 335—338° (decomp.), $[\alpha]_D$ +13° (*c*, 1·79) (Found : C, 77·9; H, 10·35. $C_{30}H_{48}O_3,CH_3{\cdot}OH$ requires C, 77·45; H, 10·65%).

Treatment of oleanolic acid with hydrochloric and acetic acids, or with hydrogen bromide (50%) in acetic acid, according to the directions of Winterstein and Stein (*Z. physiol. Chem.*, 1931, **199**, 64) afforded 18-*iso*oleanolic lactone acetate (previously described as " oleanolic acid lactone acetate "), m. p. 350—353° (decomp.) (from chloroform–methanol), $[\alpha]_D$ +23° (*c*, 1·20), in excellent yield. There was no depression in m. p. on admixture with authentic 18-*iso*-lactone acetate. Similar treatment of oleanolic lactone (see above) with hydrogen bromide in acetic acid likewise afforded the 18-*iso*-lactone acetate in good yield.

Lactonisation of Morolic Acid.—Morolic acid (1·0 g.) in 50% hydrogen bromide–acetic acid (20 ml.) was left for 4 days at room temperature. Dilution with water gave 18-*iso*oleanolic

lactone acetate (375 mg.) (recrystallised from chloroform–methanol), m. p. 345—350° (decomp.), $[\alpha]_D$ +23° (*c*, 1·24), +22° (*c*, 1·90). The mixed m. p. with authentic material was undepressed at 341—346° (decomp.). Hydrolysis of the acetate (110 mg.) in the usual way and oxidation of the product with chromium trioxide (25 mg.) in " AnalaR " acetic acid gave 18-iso*oleanonic lactone* (recrystallised from chloroform–methanol), m. p. 323—325° (decomp.), $[\alpha]_D$ +35° (*c*, 1·10) (Found: C, 77·8; H, 10·1. $C_{30}H_{46}O_3,0{\cdot}5CH_3{\cdot}OH$ requires C, 77·85; H, 10·3%).

12-*Hydroxyoleanolic Acetate Lactone.*—(*a*) *Use of perhydrol–acetic acid* (Ruzicka, Hösli, and Hofmann, *Helv. Chim. Acta*, 1936, **19**, 109). Oleanolic acid acetate (1·0 g.) in acetic acid (40 ml.) was treated on the steam-bath with a mixture of acetic acid (12 ml.) and perhydrol (12 ml.). Addition of hot water (20 ml.) gave the crystalline 12-hydroxyoleanolic acetate lactone (530 mg.), further purified by recrystallisation from chloroform–methanol. For physical data see the Table below.

(*b*) *Use of perbenzoic acid* (Picard and Spring, *J.*, 1940, 1387). Oleanolic acid acetate (670 mg.) in 40 ml. of 0·15 N-perbenzoic acid solution in chloroform was left for 17 days at 0°. The uptake of perbenzoic acid was 115% of theory. Working up in the usual way gave the 12-hydroxy-lactone with the properties recorded below.

Method of prep. of 12-hydroxy-oleanolic acetate lactone.	12-Hydroxy-lactone, m. p.*†	$[\alpha]_D$	12-Acetoxy-lactone, m. p.*	$[\alpha]_D$
(*a*) Perhydrol–acetic acid	296—297°; then 317—327° (decomp.)	+47° (*c*, 2·52)	275–285° (decomp.)	+62° (*c*, 0·98)
(*b*) Perbenzoic acid	296—297°; then 327—330° (decomp.)	+44° (*c*, 1·71)	274—282° (decomp.)	+60° (*c*, 1·07)
(*c*) Potassium permanganate	293°; then 322—324° (decomp.)	+42° (*c*, 1·23)	272—282° (decomp.)	+59° (*c*, 1·75

* The appropriate mixed m.p.s showed no depression.
† Taken in evacuated capillaries.

(*c*) *Use of potassium permanganate* (Aumüller, Wedekind, and Schicke, *Annalen*, 1935, **517**, 211). Oleanolic acid acetate (2·5 g.) in " AnalaR " acetone (200 ml.) and 2N-aqueous sulphuric acid (12·5 ml.) was oxidised at reflux temperature by the addition of a saturated solution of potassium permanganate (5 g.) in acetone. Working up in the usual way gave the 12-hydroxy-lactone (800 mg.) (see Table).

12-Hydroxyoleanolic acetate lactone (190 mg.), treated with pyridine (8 ml.) and acetic anhydride (3 ml.) at room temperature overnight, was recovered unchanged. However, heating at 100° for 1·5 hours with the same reagent gave the diacetate, recrystallised from chloroform–methanol. In a further experiment the heating time was ½ hour. These conditions also produced complete acetylation.

Methyl Olean-10-enolate Acetate.—Methyl 12-keto-olean-10-enolate acetate, m. p. 202—204°, $[\alpha]_D$ +53° (*c*, 2·10), +53° (*c*, 1·82), $\lambda_{max.}$ 247 mμ, $\varepsilon_{max.}$ 10,600, was prepared both by Picard and Spring's method (*J.*, 1939, 1045) and by Ruzicka, Jeger, and Winter's (*Helv. Chim. Acta*, 1943, **26**, 265). Although the latter procedure is more expeditious the former method gave better yields.

Methyl 12-keto-olean-10-enolate acetate (1·07 g.) was hydrogenated in " AnalaR " acetic acid (50 ml.) at room temperature over a platinum catalyst for 15 hours. Worked up in the usual way the product of the reaction was chromatographed over alumina. Benzene–light petroleum (1 : 9) removed only a trace of oil, but a 1 : 3 mixture was effective. An early fraction gave, on recrystallisation from methanol, long needles of *methyl olean-10-enolate acetate*, m. p. 190—192°, $[\alpha]_D$ +52° (*c*, 1·27), $\lambda_{max.}$ 199 mμ, $\varepsilon_{max.}$ 3500, ε_{215} 350 (*c*, 0·0093) (Found: C, 77·15; H, 10·1. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%); there was no indication of any selective absorption at 282 mμ. Final elution with benzene alone gave material which, recrystallised from chloroform–methanol, afforded methyl olean-10 : 12-dienolate acetate, m. p. 207—209°, $[\alpha]_D$ +244° (*c*, 2·14), +242° (*c*, 1·25), $\lambda_{max.}$ 282 mμ, $\varepsilon_{max.}$ 9800 (Found: C, 77·75; H, 9·65. Calc. for $C_{33}H_{50}O_4$: C, 77·6; H, 9·85%).

Methyl olean-10-enolate acetate was more conveniently prepared in the following way. Methyl 12-keto-olean-10-enolate acetate (2·0 g.) was heated with sodium (1·7 g.) dissolved in absolute ethanol (15 ml.) and 95% hydrazine (8 ml.) in a sealed tube at 180° for 18 hours. After working up in the usual way the acid product was methylated, acetylated, and then chromatographed over alumina (9 fractions). Elution with 40 : 60 and 50 : 50 benzene–light petroleum gave, after recrystallisation from methanol, 500 mg. of the required acetate methyl ester.

Reduction of 11-*Keto-oleanolic Acid Acetate.*—11-Keto-oleanolic acid acetate (450 mg.)

ethanol (18 ml.) was refluxed (oil-bath) and sodium (1·3 g.) added during ½ hour. The reaction product was worked up in the usual way, methylated, and acetylated with refluxing acetic anhydride and sodium acetate. Chromatography over alumina gave methyl olean-10 : 12-dienolate acetate; eluted with light petroleum and crystallised from chloroform-methanol, it had $[\alpha]_D$ +243° (*c*, 0·82) and m. p. 208—210° alone or mixed with the diene, m. p. 208—210°, obtained by the catalytic hydrogenation reported above. Kitsato (see Elsevier's "Encyclopaedia of Organic Chemistry," Vol. XIV, p. 546) recorded m. p. 225—228°, $[\alpha]_D$ +230°, for this compound; we have not been able to duplicate this high m. p.

Methyl 11-*Keto-oleananolate Acetate*.—Methyl olean-10-enolate acetate (450 mg.) in "AnalaR" acetic acid (45 ml.) was treated with a mixture of perhydrol (7 ml.) and acetic acid (7 ml.) added during 2 hours whilst being heated on the steam-bath. Worked up in the usual way the reaction product had m. p. 260—272°. Recrystallisation from chloroform–methanol furnished *methyl* 11-*keto-oleananolate acetate*, m. p. 272—274°, $[\alpha]_D$ +3° (*c*, 3·05), +4° (*c*, 1·34), $\lambda_{max.}$ 292 mμ, $\epsilon_{max.}$ 30 (Found: C, 74·8; H, 9·8. $C_{33}H_{52}O_5$ requires C, 74·95; H, 9·9%). This compound also crystallises in a different form, m. p. 255—257°.

When methyl 11-keto-oleananolate acetate (75 mg.) was heated with sodium (100 mg.) dissolved in ethanol (2 ml.) and 95% hydrazine (1 ml.) at 180° for 18 hours, the product, after remethylation and reacetylation, was characterised as starting material by m. p. and mixed m. p.

2 : 28-*Diacetoxyoleanan*-11-*ol*.—Lithium aluminium hydride (450 mg.) was refluxed for 5 minutes in sodium-dried ether (10 ml.), and the solution rapidly filtered into a solution of methyl 11-keto-oleananolate acetate (100 mg.) in dry ether (20 ml.). After 1 hour's refluxing the excess of lithium aluminium hydride was destroyed by addition of a few drops of ethyl acetate. The reaction mixture was then diluted with water, acidified with dilute sulphuric acid, and worked up in the usual way. Recrystallisation of the product from aqueous methanol furnished fine short needles of oleanane-2 : 11 : 28-triol, softening at 120°, clearing of bubbles at 127°, and mobile at 145°, $[\alpha]_D$ +19° (*c*, 1·20). The triol was acetylated overnight at room temperature, with pyridine and acetic anhydride. Working up in the usual way gave a crude product, m. p. 241—245°; recrystallised from methanol containing a few drops of chloroform it afforded 2 : 28-*diacetoxyoleanan*-11-*ol*, m. p. 267—270°, $[\alpha]_D$ +31° (*c*, 1·50) (Found: C, 74·85; H, 9·9. $C_{34}H_{56}O_5$ requires C, 74·95; H, 10·35%).

Conversion into the triacetate was effected in the following way. The triol diacetate (25 mg.) was heated with acetic anhydride (0·5 ml.) and pyridine (3 ml.) at 100° for 5 hours. Working up the dark product in the usual way, and filtration in benzene solution through alumina, gave 2 : 11 : 28-*triacetoxyoleanane* (20 mg.) which, recrystallised from methanol, had m. p. 275—277°, $[\alpha]_D$ +55° (*c*, 0·87) (Found: C, 73·35; H, 9·8. $C_{36}H_{58}O_6$ requires C, 73·7; H, 9·95%). In comparable experiments 75 mg. of the diacetate gave 10 mg. of the triacetate (1 hour's heating) and 23 mg. of the diacetate afforded 8 mg. of the triacetate (2 hours' heating).

2 : 28-*Diacetoxyoleanan*-11-*one*.—2 : 28-Diacetoxyoleanan-11-ol (100 mg.) in "AnalaR" acetic acid (3 ml.) was oxidised with chromium trioxide (70 mg.), and the solution left overnight at room temperature. Working up in the usual way, and filtration in benzene solution through alumina, gave 2 : 28-*diacetoxyoleanan*-11-*one* which, recrystallised from methanol, had m. p. 260—262°, $[\alpha]_D$ +6° (*c*, 1·41) (Found: C, 74·55; H, 9·9. $C_{34}H_{54}O_5$ requires C, 75·25; H, 10·0%). There was a marked depression in m. p. on admixture with starting material.

2 : 28-*Diacetoxyolean*-10-*ene*.—(a) *From methyl olean*-10-*enolate acetate*. The methyl ester acetate (50 mg.) was refluxed for ½ hour with a filtered solution of lithium aluminium hydride (300 mg.) in dry ether (50 ml.). Working up as above, and acetylation of the product with pyridine and acetic anhydride at 100° for ½ hour, afforded 2 : 28-*diacetoxyolean*-10-*ene* (recrystallised from methanol), m. p. 204—205°, $[\alpha]_D$ +59° (*c*, 1·03) (Found: C, 77·15; H, 10·25. $C_{34}H_{54}O_4$ requires C, 77·5; H, 10·35%).

(b) *By dehydration of* 2 : 28-*diacetoxyoleanan*-11-*ol*. The triol diacetate (25 mg.) in dry pyridine (3 ml.) was treated with redistilled phosphorus oxychloride (0·3 ml.), and the solution heated for 3 hours at 100°. Dilution with water, extraction with ether, and working up in the usual way, furnished 2 : 28-diacetoxyolean-10-ene; recrystallised from methanol, this had m. p. 200—202°, $[\alpha]_D$ +56° (*c*, 0·99). The mixed m. p. with authentic material (m. p. 204—205°; see above) was 201—203°.

Methyl 19-*Keto-oleananolate Acetate*.—Methyl dihydrosiaresinolate acetate (110 mg.), prepared as described before (Barton, Brooks, and Holness, *J.*, 1951, 277) in "AnalaR" acetic acid (20 ml.) was treated with chromium trioxide (25 mg.) in 95% "AnalaR" acetic acid (25 ml.) and left overnight. Working up in the usual way and recrystallisation from methanol

afforded *methyl* 19-*keto-oleananolate acetate*, m. p. 228—230°, $[\alpha]_D$ +46° (*c*, 1·83) (Found : C, 75·1; H, 9·7. $C_{33}H_{52}O_5$ requires C, 74·95; H, 9·95%).

Methyl 19-*Keto*-18-iso*oleananolate Acetate.*—Methyl 19-keto-oleananolate acetate (80 mg.) was refluxed for 1 hour with 10% methanolic potassium hydroxide (20 ml.). Working up in the usual way gave *methyl* 19-*keto*-18-iso*oleananolate*, m. p. 274—275° (from methanol), $[\alpha]_D$ +52° (*c*, 1·20) (Found : C, 76·85; H, 10·7. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·35%). Acetylation by pyridine–acetic anhydride overnight and working up in the usual way afforded *methyl* 19-*keto*-18-iso*oleananolate acetate*, m. p. 285—287° (from methanol), $[\alpha]_D$ +53° (*c*, 1·40) (Found : C, 74·65; H, 9·85. $C_{33}H_{52}O_5$ requires C, 74·95; H, 9·95%).

2 : 28-*Diacetoxyoleanan*-19-*ol.*—Methyl dihydrosiaresinolate acetate (250 mg.) in dry ether (40 ml.) was refluxed with a filtered solution of lithium aluminium hydride (750 mg.) in dry ether (30 ml.) for 2·5 hours. Decomposition of the excess of lithium aluminium hydride with excess of ethyl acetate, acidification with dilute sulphuric acid, working up in the usual way, and finally acetylation (pyridine–acetic anhydride at 100° for 30 minutes) afforded 2 : 28-*diacetoxyoleanan*-19-*ol* which, recrystallised from chloroform–methanol, had m. p. 255—256°, $[\alpha]_D$ +23° (*c*, 1·69) (Found : C, 74·8; H, 10·35. $C_{34}H_{56}O_5$ requires C, 75·0; H, 10·35%).

2 : 28-*Diacetoxyoleanan*-19-*one.*—2 : 28-Diacetoxyoleanan-19-ol (60 mg.) in " AnalaR " acetic acid (10 ml.) was left overnight at room temperature with chromium trioxide (15 mg.) in 95% acetic acid (2 ml.). Working up in the usual way and recrystallisation from chloroform–methanol furnished 2 : 28-*diacetoxyoleanan*-19-*one*, m. p. 246—248°, $[\alpha]_D$ +50° (*c*, 1·00) (Found : C, 75·15; H, 10·15. $C_{34}H_{54}O_5$ requires C, 75·25; H, 10·05%).

This compound (50 mg.) was refluxed with 30% methanolic potassium hydroxide (20 ml.) for 2 hours. After working up in the usual way, acetylation (pyridine–acetic anhydride overnight at room temperature) and repeated recrystallisation from methanol gave 2 : 28-*diacetoxy*-18-iso*oleanan*-19-*one*, m. p. 214—216° (Found : C, 75·25; H, 9·85. $C_{34}H_{54}O_5$ requires C, 75·25; H, 10·05%).

2 : 28-*Diacetoxy*-18-iso*oleanan*-19-*ol.*—Methyl 19-keto-18-*iso*oleananolate acetate (240 mg.) (see above) in dry ether (30 ml.) was refluxed with a filtered solution of lithium aluminium hydride (600 mg.) in dry ether (20 ml.) for 1·5 hours. Working up in the usual way and acetylation with acetic anhydride–pyridine for 3 hours at room temperature furnished 2 : 28-diacetoxy-18-*iso*oleanan-19-ol (" betulin triol diacetate ") which, recrystallised from chloroform–methanol, had m. p. 239—241°, $[\alpha]_D$ +25° (*c*, 0·61). This gave no depression in m. p. on admixture with an authentic specimen of " betulin triol diacetate," m. p. 240—242°, $[\alpha]_D$ +22° (*c*, 0·78), kindly supplied by Professor E. R. H. Jones, F.R.S., and Dr. T. G. Halsall.

Oxidation of 2 : 28-diacetoxy-18-*iso*oleanan-19-ol with chromium trioxide in aqueous acetic acid in the usual way, followed by chromatography (11 fractions), gave 2 : 28-diacetoxy-18-*iso*-oleanan-19-one (recrystallised from methanol), m. p. 216—218°, $[\alpha]_D$ +41° (*c*, 1·13). There was no depression in m. p. on admixture with (*a*) the same compound (m. p. 214—216°) prepared by the alternative route given above or (*b*) the ketone of the same m. p. and $[\alpha]_D$ +37° (*c*, 0·90) prepared by Davy, Halsall, Jones, and Meakins (*loc. cit.*) by oxidation of " betulin triol diacetate." We thank Professor Jones and Dr. Halsall for carrying out the mixed m. p. determination.

Effect of Alkali on Methyl 12-*Keto-oleananolate Acetate.*—The methyl ester acetate (150 mg.) was refluxed with 10% (w/v) methanolic potassium hydroxide (10 ml.) for 1 hour. Worked up in the usual way the product was acetylated (pyridine–acetic anhydride overnight at room temperature). Recrystallisation gave unchanged starting material, m. p. 191—193° alone or mixed with authentic methyl ester acetate of the same m. p. This experiment shows that $C_{(13)}$ is not inverted by the action of potassium hydroxide.

Derivatives of Moradiol.—Moradiol (Barton and Brooks, *J.*, 1951, 257) (100 mg.) in glacial acetic acid (10 ml.) was treated with 2 drops of concentrated sulphuric acid and heated for 3 hours on the steam-bath. Working up in the usual way and recrystallisation from chloroform–methanol furnished moradiol diacetate, m. p. 273° alone or mixed with authentic material of the same m. p.

Under the same conditions betulin was converted almost quantitatively into *allo*betulin acetate, m. p. 280—282°.

Moradiol (250 mg.) was refluxed with 100% formic acid (5 ml.). A thick paste of crystals was rapidly deposited. Working up in the usual way and recrystallisation from chloroform–methanol furnished *moradiol diformate*, m. p. 284—286°, $[\alpha]_D$ +22° (*c*, 1·57) (Found : C, 77·55; H, 10·2. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%). Alkaline hydrolysis gave back moradiol (mixed m. p.).

Betulin (1 g.), treated with 100% formic acid (9 ml.) in the same way, gave *allo*betulin formate, m. p. 310—312° (decomp.) (in an evacuated capillary) (cf. Schulze and Pieroh, *Ber.*, 1922, **55**, 2332).

Moradiol Oxide.—Moradiol diacetate oxide (Barton and Brooks, *loc. cit.*) (200 mg.) was refluxed with 10% (w/v) methanolic potassium hydroxide (20 ml.) for 1 hour. Working up in the usual way and crystallisation from aqueous methanol gave *moradiol oxide*, m. p. 205—207° (decomp.), $[\alpha]_D$ +21° (*c*, 4·00) (Found: C, 78·2; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%). Acetylation with pyridine–acetic anhydride at room temperature overnight gave back moradiol diacetate oxide, m. p. 255—256° alone or mixed with an authentic specimen of the same m. p.

Ursolic Lactone.—Ursolic acid (315 mg.), m. p. 282—283°, $[\alpha]_D$ +72° (*c*, 1·45), extracted from bearberry leaves, was treated in chloroform with hydrogen chloride, as for oleanolic acid (see above). Separation of the equilibrated product furnished a neutral fraction (28 mg., 9%), recrystallised from methanol to give *ursolic lactone*, m. p. 256—258°, $[\alpha]_D$ +4° (*c*, 1·43), no absorption of $E^{1\%}_{1\,cm.} > 1$ in the 195—350-mμ region (Found: C, 79·5; H, 10·2. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). The acid fraction was characterised as unchanged ursolic acid. A second experiment showed 12% of lactone in the equilibrium mixture.

Acetylation of the lactone with pyridine–acetic anhydride overnight at room temperature gave the corresponding acetate, m. p. 252—254° (from methanol), $[\alpha]_D$ +14° (*c*, 1·42), +13° (*c*, 0·76) (Found: C, 77·85; H, 10·35. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·0%).

Experiments with Methyl 11-Ketoursolate Acetate.—Methyl 11-ketoursolate acetate (250 mg.) m. p. 240—242°, $[\alpha]_D$ +81° (*c*, 2·12), $\lambda_{max.}$ 249 mμ, $\varepsilon_{max.}$ 12 400, prepared according to the directions of Ewen and Spring (*J.*, 1943, 523), was treated with 20% ethanolic potassium hydroxide (5 ml.) at 180° for 24 hours. Working up in the usual way, methylation, reacetylation, and recrystallisation from methanol, gave unchanged starting material (190 mg.), m. p. 240—242° (mixed m. p.).

In a comparable experiment 1·5 g. of the ketone was kept with 50% hydrogen bromide–acetic acid (20 ml.) at room temperature for 7 days. Working up in the usual way, filtration in benzene solution through alumina, and recrystallisation from methanol gave back unchanged starting material (740 mg.), m. p. and mixed m. p. 236—239°, $[\alpha]_D$ +81° (*c*, 0·95).

Methyl Oleanolate Chloroacetate [with G. F. Laws].—A solution of methyl oleanolate (850 mg.) in dry pyridine (25 ml.) was cooled to −30° and chloroacetyl chloride (2·6 g., 1·75 ml.) added dropwise with shaking. The solution was left without further cooling for ½ hour and then worked up in the usual way. After filtration through alumina in benzene solution and recrystallisation from chloroform–methanol, *methyl oleanolate chloroacetate* was obtained, having m. p. 190—191° (Found: Cl, 6·8. $C_{33}H_{51}O_4Cl$ requires Cl, 6·5%).

Methyl Oleanolate Iodoacetate [with G. F. Laws].—Methyl oleanolate chloroacetate (350 mg.) in acetone (25 ml.) was refluxed with powdered potassium iodide (1 g.) for 3 hours. Working up in the usual way, followed by filtration through alumina in benzene solution and crystallisation from chloroform–methanol, afforded fine white needles of *methyl oleanolate iodoacetate*, m. p. 110° (decomp.) (Found: I, 19·8. $C_{33}H_{51}O_4I$ requires I, 19·9%).

2 : 28-*Diacetoxyolean*-11 : 13(18)-*diene.*—A filtered solution of lithium aluminium hydride (200 mg.) in dry ether (20 ml.) was added to methyl dehydro-oleanolate acetate (100 mg.) in dry ether (10 ml.). The mixture was refluxed for 0·5 hour, worked up in the usual way, and acetylated with acetic anhydride (1 ml.) and pyridine (3 ml.) overnight at room temperature. Working up in the usual way afforded 2 : 28-*diacetoxyolean*-11 : 13(18)-*diene* (dehydroerythrodiol diacetate) which, recrystallised from methanol, had m. p. 214—215°, $[\alpha]_D$ −87° (*c*, 1·39), $\lambda_{max.}$ 240, 250, and 260 mμ, $\varepsilon_{max.}$ 25,000, 29,000, and 19,500 respectively (Found: C, 77·55; H, 10·05. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%). This was also prepared by reduction of methyl 11-keto-oleanolate acetate (250 mg.) in dry ether (30 ml.) with lithium aluminium hydride (500 mg.) in dry ether (30 ml.), refluxing for 0·5 hour. Working up in the usual way, and acetylation by refluxing with acetic anhydride (10 ml.) for 2 hours, gave the same diacetate, m. p. and mixed m. p. 215—216°.

β-*Amyranonyl Benzoate.*—β-Amyrin benzoate (2 g.) in acetic acid (150 ml.) was heated on the steam-bath and treated dropwise during 0·5 hour with a mixture of acetic acid (40 ml.) and perhydrol (40 ml.). The resulting solution was kept at 100° for 1·5 hours. Hot water was then added until turbidity appeared. After cooling to room temperature, the crystals were filtered off and recrystallised from chloroform–methanol, to give β-amyranonyl benzoate, m. p. 252—254°, $[\alpha]_D$+1 2° (*c*, 1·47) (Found: C, 80·55; H, 9·85. Calc. for $C_{37}H_{54}O_3$: C, 81·25; H, 9·95%) (cf. Simpson, *J.*, 1940, 235). That this was a ketone and not an oxide

was proved in two ways. First, heating the benzoate (50 mg.) in acetic acid (10 ml.) and concentrated hydrochloric acid (5 ml.) on the steam-bath for 15 minutes gave the starting material unchanged (m. p. and mixed m. p.). Secondly, alkaline hydrolysis of the benzoate (50 mg.), followed by acetylation, gave β-amyranonyl acetate, m. p. 293—295°, $[\alpha]_D$ −11° (*c*, 1·88). Spring (*J.*, 1933, 1345) gives m. p. 291—292° for this compound.

Reduction of β-Amyranonyl Benzoate.—β-Amyranonyl benzoate (500 mg) in *n*-propyl alcohol (20 ml.) was heated at 130° (oil-bath temp.) and treated during 1 hour with a large excess of sodium (2 g.), the bath temperature being gradually raised to 180°. A further 10 ml. of *n*-propyl alcohol was added, followed by more sodium (0·5 g.). The excess of sodium was destroyed by addition of more *n*-propyl alcohol, and the mixture was then worked up in the usual way. Recrystallisation from methanol gave *β-amyrane-2 : 12-diol*, m. p. 207—208°, $[\alpha]_D$ +6° (*c*, 1·40), +6° (*c*, 1·29) (Found : C, 81·05; H, 11·4. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). The diol (25 mg.) in pyridine (2 ml.) and acetic anhydride (1 ml.) was left overnight at room temperature. Working up in the usual way and recrystallisation from aqueous methanol furnished *2 : 12-diacetoxy-β-amyrane*, m. p. 194—195°, $[\alpha]_D$ +11° (*c*, 0·97), +12° (*c*, 0·55) (Found : C, 77·5; H, 10·65. $C_{34}H_{56}O_4$ requires C, 77·3; H, 10·65%). The acetylation was also accomplished more expeditiously by acetic anhydride and pyridine on the steam-bath (1 hour).

These compounds, with equatorial hydroxyl groups at both $C_{(2)}$ and $C_{(12)}$, were reported previously by Picard, Sharples, and Spring (*J.*, 1939, 1045) to have the following constants : β-amyrane-2 : 12-diol, m. p. 216—217°, $[\alpha]_D$ +97°; its derived diacetate, m. p. 183—184°, $[\alpha]_D$ +42°. At the present time we are unable to explain this discrepancy. As further evidence for the correctness of the physical constants now reported, β-amyranonyl benzoate (see above) was hydrolysed to β-amyranonol, which was then reduced with sodium and *n*-propyl alcohol, as described above for the benzoate. The product was the β-amyrane-2 : 12-diol, m. p. 204—206°, $[\alpha]_D$ +8° (*c*, 1·52), identical (mixed m. p.) with the diol prepared by reduction of the benzoate (see above).

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and the Chemical Society for financial assistance. This work was carried out during the tenure of a D.S.I.R. Maintenance Grant to one of us (N. J. H.). We also thank Mr. C. J. W. Brooks and Mr. A. W. Burgstahler (Harvard) for stimulating discussions.

BIRKBECK COLLEGE, LONDON, W.C.1 [*Received, August 8th*, 1951.]